(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068774 A1

(51) International Patent Classification[7]: C07D 471/14 // A61K 31/4375, A61P 1/00, (C07D 471/14, 235:00), 221:00)

(21) International Application Number: PCT/EP03/01349

(22) International Filing Date: 12 February 2003 (12.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02003536.6 15 February 2002 (15.02.2002) EP

(71) Applicant *(for all designated States except US)*: **ALTANA PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BUHR, Wilm** [DE/DE]; Zum Kirchenwald 7, 78465 Konstanz (DE). **SENN-BILFINGER, Jörg** [DE/DE]; Säntisstrasse 7, 78464 Konstanz (DE). **ZIMMERMANN, Peter, Jan** [DE/DE]; Zum Lerchental 43/1, 78315 Radolfzell (DE). **ZIMMERMANN, Peter** [DE/DE]; Radolfzeller Str. 71a, 78467 Konstanz (DE).

(74) Common Representative: **ALTANA PHARMA AG**; Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

(81) Designated States *(national)*: AE, AL, AU, BA, BR, CA, CN, CO, CU, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, RO, SG, TN, UA, US, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AL, AU, BA, BR, CA, CN, CO, CU, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, RO, SG, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *of inventorship (Rule 4.17(iv)) for US only*

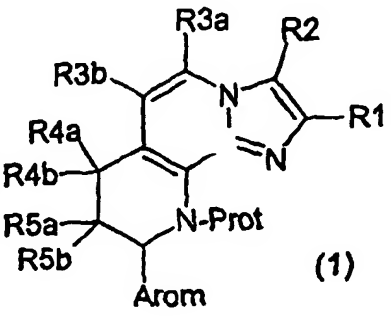
Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/068774 A1

(54) Title: TRICYCLIC N-ACYL COMPOUNDS



(1)

(57) Abstract: The invention relates to compounds of the formula (1) where the substituents and symbols are as defined in the description. The compounds are valuable intermediates for preparing active pharmaceutical ingredients.

TRICYCLIC N-ACYL COMPOUNDS

Technical field

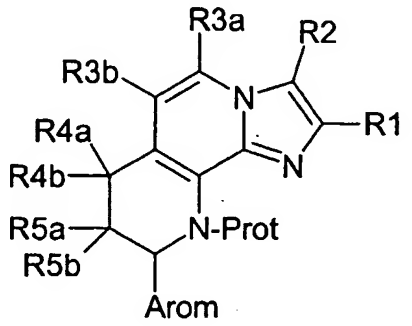
The invention relates to novel compounds which are used in the pharmaceutical industry as valuable intermediates for preparing active ingredients.

Prior art

The International Patent Applications WO 98/42707, WO 00/17200, WO 00/26217, WO 00/63211, WO 01/72756, WO 01/72754, WO 01/72757 and WO 02/34749 disclose tricyclic imidazopyridine derivatives having very particular substitution patterns which are said to be suitable for treating gastric and intestinal diseases.

Description of the invention

The invention provides compounds of the formula 1



(1)

where

R1 is hydrogen, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkoxycarbonyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, fluoro-C_{1-4}-alkyl or hydroxy-C_{1-4}-alkyl,

R2 is hydrogen, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-4}-alkyl, C_{1-4}-alkoxycarbonyl, hydroxy-C_{1-4}-alkyl, halogen, C_{2-4}-alkenyl, C_{2-4}-alkynyl, fluoro-C_{1-4}-alkyl or cyanomethyl,

R3a is hydrogen, halogen, fluoro-C_{1-4}-alkyl, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{1-4}-alkoxy, carboxyl, C_{1-4}-alkoxycarbonyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkoxy-C_{1-4}-alkyl, fluoro-C_{1-4}-alkoxy-C_{1-4}-alkyl or the -CO-NR31R32 radical,

R3b is hydrogen, halogen, fluoro-C_{1-4}-alkyl, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{1-4}-alkoxy, carboxyl, C_{1-4}-alkoxycarbonyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkoxy-C_{1-4}-alkyl, fluoro-C_{1-4}-alkoxy-C_{1-4}-alkyl or the -CO-NR31R32 radical,

where

R31 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl and

R32 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which they are both bonded, are a pyrrolidino, piperidino or morpholino radical,

R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where

R41 is a suitable oxygen protecting group,

or where

R4a is hydroxyl, and R5a, R4b and R5b are each hydrogen,

Arom is a mono- or bicyclic aromatic radical which is substituted by R6, R7, R8 and R9 and is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,

where

R6 is hydrogen, C_{1-4}-alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{2-4}-alkenyloxy, C_{1-4}-alkylcarbonyl, carboxyl, C_{1-4}-alkoxycarbonyl, carboxy-C_{1-4}-alkyl, C_{1-4}-alkoxycarbonyl-C_{1-4}-alkyl, halogen, hydroxyl, aryl, aryl-C_{1-4}-alkyl, aryloxy, aryl-C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, mono- or di-C_{1-4}-alkylamino, C_{1-4}-alkylcarbonylamino, C_{1-4}-alkoxycarbonylamino, C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonylamino or sulphonyl,

R7 is hydrogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

R8 is hydrogen, C_{1-4}-alkyl or halogen and

R9 is hydrogen, C_{1-4}-alkyl or halogen,

where

aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group of C_{1-4}-alkyl, C_{1-4}-alkoxy, carboxyl, C_{1-4}-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

Prot is an amino protecting group,

and their salts.

C_{1-4}-Alkyl represents straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples include the butyl, iso-butyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

C_{3-7}-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which preference is given to cyclopropyl, cyclobutyl and cyclopentyl.

C_{3-7}-Cycloalkyl-C_{1-4}-alkyl represents one of the abovementioned C_{1-4}-alkyl radicals which is substituted by one of the abovementioned C_{3-7}-cycloalkyl radicals. Examples include the cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl radicals.

C_{1-4}-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples include the butoxy, iso-butoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

C_{1-4}-Alkoxy-C_{1-4}-alkyl represents one of the abovementioned C_{1-4}-alkyl radicals which is substituted by one of the abovementioned C_{1-4}-alkoxy radicals. Examples include the methoxymethyl, methoxyethyl and butoxyethyl radicals.

C_{1-4}-Alkoxycarbonyl (-CO-C_{1-4}-alkoxy) represents a carbonyl group to which one of the abovementioned C_{1-4}-alkoxy radicals is bonded. Examples include the methoxycarbonyl (CH_3O-C(O)-) and ethoxycarbonyl (CH_3CH_2O-C(O)-) radicals.

C_{2-4}-Alkenyl represents straight-chain or branched alkenyl radicals having 2 to 4 carbon atoms. Examples include the 2-butenyl, 3-butenyl, 1-propenyl and 2-propenyl (allyl) radicals.

C_{2-4}-Alkynyl represents straight-chain or branched alkynyl radicals having 2 to 4 carbon atoms. Examples include the 2-butynyl, 3-butynyl and preferably the 2-propynyl (propargyl) radicals.

Fluoro-C_{1-4}-alkyl represents one of the abovementioned C_{1-4}-alkyl radicals which is substituted by one or more fluorine atoms. An example is the trifluoromethyl radical.

Hydroxy-C_{1-4}-alkyl represents the abovementioned C_{1-4}-alkyl radicals which are substituted by a hydroxyl group. Examples include the hydroxymethyl, 2-hydroxyethyl and 3-hydroxypropyl radicals.

For the purposes of the invention, halogen is bromine, chlorine and fluorine.

C_{1-4}-Alkoxy-C_{1-4}-alkoxy represents one of the abovementioned C_{1-4}-alkoxy radicals which is substituted by a further C_{1-4}-alkoxy radical. Examples include the 2-(methoxy)ethoxy (CH_3-O-CH_2-CH_2-O-) and 2-(ethoxy)ethoxy (CH_3-CH_2-O-CH_2-CH_2-O-) radicals.

C_{1-4}-Alkoxy-C_{1-4}-alkoxy-C_{1-4}-alkyl represents one of the abovementioned C_{1-4}-alkoxy-C_{1-4}-alkyl radicals which is substituted by one of the abovementioned C_{1-4}-alkoxy radicals. An example is the 2-(methoxy)ethoxymethyl (CH_3-O-CH_2-CH_2-O-CH_2-) radical.

Fluoro-C_{1-4}-alkoxy-C_{1-4}-alkyl represents one of the abovementioned C_{1-4}-alkyl radicals which is substituted by a fluoro-C_{1-4}-alkoxy radical. Fluoro-C_{1-4}-alkoxy represents one of the abovementioned C_{1-4}-alkoxy radicals which is predominantly or fully substituted by fluorine. Examples of predominantly or fully fluorine-substituted C_{1-4}-alkoxy include the 1,1,1,3,3,3-hexafluoro-2-propoxy, 2-trifluoromethyl-2-propoxy, 1,1,1-trifluoro-2-propoxy, perfluoro-tert-butoxy, 2,2,3,3,4,4,4-heptafluoro-1-butoxy, 4,4,4-trifluoro-1-butoxy, 2,2,3,3,3-pentafluorpropoxy, perfluoroethoxy or 1,2,2-trifluoroethoxy radicals, in particular the 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy or trifluoromethoxy radicals, and preferably the difluoromethoxy radical.

C_{1-7}-Alkyl represents straight-chain or branched alkyl radicals having 1 to 7 carbon atoms. Examples include the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethyl-

butyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, iso-butyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

C_{2-4}-Alkenyloxy represents a radical which, in addition to the oxygen atom, contains a C_{2-4}-alkenyl radical. An example is the allyloxy radical.

C_{1-4}-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned C_{1-4}-alkyl radicals. An example is the acetyl radical.

An example of carboxy-C_{1-4}-alkyl is the carboxymethyl ($-CH_2COOH$) or the carboxyethyl ($-CH_2CH_2COOH$) radical.

C_{1-4}-Alkoxycarbonyl-C_{1-4}-alkyl represents one of the abovementioned C_{1-4}-alkyl radicals which is substituted by one of the abovementioned C_{1-4}-alkoxycarbonyl radicals. An example is the ethoxycarbonylmethyl radical ($CH_3CH_2OC(O)CH_2-$).

Aryl-C_{1-4}-alkyl represents an aryl-substituted C_{1-4}-alkyl radical. An example is the benzyl radical.

Aryl-C_{1-4}-alkoxy represents an aryl-substituted C_{1-4}-alkoxy radical. An example is the benzyloxy radical.

In addition to the nitrogen atom, mono- or di-C_{1-4}-alkylamino radicals contain one or two of the abovementioned C_{1-4}-alkyl radicals. Preference is given to di-C_{1-4}-alkylamino and in particular dimethyl-, diethyl- or diisopropylamino.

C_{1-4}-Alkylcarbonylamino represents an amino group to which is bonded a C_{1-4}-alkylcarbonyl radical. Examples include the propionylamino ($C_3H_7C(O)NH-$) and the acetylamino (acetamido) ($CH_3C(O)NH-$) radicals.

C_{1-4}-Alkoxycarbonylamino represents an amino radical which is substituted by one of the abovementioned C_{1-4}-alkoxycarbonyl radicals. Examples include the ethoxycarbonylamino and methoxycarbonylamino radicals.

C_{1-4}-Alkoxy-C_{1-4}-alkoxycarbonyl represents a carbonyl group which is bonded to one of the abovementioned C_{1-4}-alkoxy-C_{1-4}-alkoxy radicals. Examples include the 2-(methoxy)ethoxycarbonyl (CH_3-O-CH_2CH_2-O-CO-) and the 2-(ethoxy)ethoxycarbonyl (CH_3CH_2-O-CH_2CH_2-O-CO-) radicals.

C_{1-4}-Alkoxy-C_{1-4}-alkoxycarbonylamino represents an amino radical which is substituted by one of the abovementioned C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonyl radicals. Examples include the 2-(methoxy)ethoxycarbonylamino and 2-(ethoxy)ethoxycarbonylamino radicals.

Useful oxygen protecting groups R41 are in principle any groups which behave in the desired manner on further conversion of the compounds of the formula 1, i.e., for example, can be converted by oxidation with suitable oxidizing agents to a keto group and by reduction with suitable reducing agents to a hydroxyl group. Examples of protecting groups include the C_{1-4}-alkoxycarbonyl, C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonyl and C_{1-4}-alkylcarbonyl radicals. In a preferred embodiment of the invention, the R41 and Prot groups are identical.

Examples of Arom radicals include the following substituents: 4-acetoxyphenyl, 4-acetamidophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 3-benzyloxy-4-methoxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3,5-bis(trifluoromethyl)phenyl, 4-butoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-chloro-6-fluorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-5-nitrophenyl, 4-chloro-3-nitrophenyl, 3-(4-chlorophenoxy)phenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 2,4-dihydroxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxy-5-hydroxyphenyl, 2,5-dimethylphenyl, 3-ethoxy-4-hydroxyphenyl, 2-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-hydroxy-5-nitrophenyl, 3-methoxy-2-nitrophenyl, 3-nitrophenyl, 2,3,5-trichlorophenyl, 2,4,6-trihydroxyphenyl, 2,3,4-trimethoxyphenyl, 2-hydroxy-1-naphthyl, 2-methoxy-1-naphthyl, 4-methoxy-1-naphthyl, 1-methyl-2-pyrrolyl, 2-pyrrolyl, 3-methyl-2-pyrrolyl, 3,4-dimethyl-2-pyrrolyl, 4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolyl, 5-ethoxycarbonyl-2,4-dimethyl-3-pyrrolyl, 3,4-dibromo-5-methyl-2-pyrrolyl, 2,5-dimethyl-1-phenyl-3-pyrrolyl, 5-carboxy-3-ethyl-4-methyl-2-pyrrolyl, 3,5-dimethyl-2-pyrrolyl, 2,5-dimethyl-1-(4-trifluoromethylphenyl)-3-pyrrolyl, 1-(2,6-dichloro-4-trifluoromethylphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(2-fluorophenyl)-2-pyrrolyl, 1-(4-trifluoromethoxyphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(4-ethoxycarbonyl)-2,5-dimethyl-3-pyrrolyl, 5-chloro-1,3-dimethyl-4-pyrazolyl, 5-chloro-1-methyl-3-trifluormethyl-4-pyrazolyl, 1-(4-chlorobenzyl)-5-pyrazolyl, 1,3-dimethyl-5-(4-chlorophenoxy)-4-pyrazolyl, 1-methyl-3-trifluoromethyl-5-(3-trifluoromethylphenoxy)-4-pyrazolyl, 4-methoxycarbonyl-1-(2,6-dichlorophenyl)-5-pyrazolyl, 5-allyloxy-1-methyl-3-trifluoromethyl-4-pyrazolyl, 5-chloro-1-phenyl-3-trifluoromethyl-4-pyrazolyl, 3,5-dimethyl-1-phenyl-4-imidazolyl, 4-bromo-1-methyl-5-imidazolyl, 2-butylimidazolyl, 1-phenyl-1,2,3-triazol-4-yl, 3-indolyl, 4-indolyl, 7-indolyl, 5-methoxy-3-indolyl, 5-benzyloxy-3-indolyl, 1-benzyl-3-indolyl, 2-(4-chlorophenyl)-3-indolyl, 7-benzyloxy-3-indolyl, 6-benzyloxy-3-indolyl, 2-methyl-5-nitro-3-indolyl, 4,5,6,7-tetrafluoro-3-indolyl, 1-(3,5-difluorobenzyl)-3-indolyl, 1-methyl-2-(4-trifluorophenoxy)-3-indolyl, 1-methyl-2-benzimidazolyl, 5-nitro-2-furyl, 5-hydroxymethyl-2-furyl, 2-furyl, 3-furyl, 5-(2-nitro-4-trifluoromethylphenyl)-2-furyl, 4-ethoxycarbonyl-5-methyl-2-furyl, 5-(2-trifluoromethoxyphenyl)-2-furyl, 5-(4-methoxy-2-nitrophenyl)-2-furyl, 4-bromo-2-furyl, 5-dimethylamino-2-furyl, 5-bromo-2-furyl, 5-sulpho-2-furyl, 2-benzofuryl, 2-thienyl, 3-thienyl, 3-methyl-2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-nitro-2-thienyl, 5-methyl-2-thienyl, 5-(4-methoxyphenyl)-2-thienyl, 4-methyl-2-thienyl, 3-phenoxy-2-thienyl, 5-carboxy-2-thienyl, 2,5-dichloro-3-thienyl, 3-methoxy-2-thienyl, 2-benzothienyl, 3-methyl-2-benzothienyl, 2-bromo-5-chloro-3-benzothienyl, 2-thiazolyl, 2-amino-4-chloro-5-thiazolyl, 2,4-dichloro-5-thiazolyl, 2-diethylamino-5-thiazolyl, 3-methyl-4-nitro-5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-methyl-2-pyridyl, 3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl, 2,6-dichloro-4-pyridyl, 3-chloro-5-trifluoromethyl-2-pyridyl, 4,6-dimethyl-2-pyridyl, 4-(4-chlorophenyl)-3-pyridyl, 2-chloro-5-methoxycarbonyl-6-methyl-4-phenyl-3-pyridyl, 2-chloro-3-pyridyl, 6-(3-trifluoromethylphenoxy)-3-pyridyl, 2-(4-chlorophenoxy)-3-pyridyl, 2,4-

dimethoxy-5-pyrimidine, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 2-chloro-3-quinolinyl, 2-chloro-6-methoxy-3-quinolinyl, 8-hydroxy-2-quinolinyl and 4-isoquinolinyl.

Useful amino protecting groups are in principle any protecting groups used for protecting amino acids in peptide and protein syntheses or for protecting other amines, for example in alkaloid or nucleotide syntheses (on this subject, see, for example, T. W. Greene and P. G. M. Wuts, Protective groups in organic synthesis, 2nd edition, 1991, John Wiley & Sons, Inc., pages 309-385). Examples of useful protecting groups include the C_{1-4}-alkylcarbonyl (for example acetyl), C_{1-4}-alkoxycarbonyl (for example butoxycarbonyl), C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonyl, benzyloxycarbonyl or nitrobenzenesulphenyl radicals. Preference is given to the acetyl radical.

Useful salts for compounds of the formula 1, depending on the substitution, are in particular all acid addition salts. Particular mention is made of the salts of the customarily used inorganic and organic acids. Useful salts are the water-soluble and water-insoluble acid addition salts with the acids, for example hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, and, depending on whether the acid is mono- or polybasic and depending on which salt is desired, the acids in the salt preparation are used in an equimolar ratio or a ratio deviating therefrom.

It is known to those skilled in the art that both the compounds according to the invention and their salts, when, for example, they are isolated in crystalline form, may contain different amounts of solvents. The invention therefore also encompasses all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1.

There are in principle three chiral centres in the basic skeleton of the compounds of the formula 1. The invention therefore provides all conceivable stereoisomers in any desired mixing ratio to one another, including the pure enantiomers which are provided with preference by the invention.

Compounds to be emphasized are those of the formula 1 where

R1 is hydrogen, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{2-4}-alkynyl or fluoro-C_{1-4}-alkyl,

R2 is hydrogen, C_{1-4}-alkyl, halogen, C_{2-4}-alkenyl, C_{2-4}-alkynyl or fluoro-C_{1-4}-alkyl,

R3a is hydrogen,

R3b is hydrogen, halogen, C_{1-4}-alkyl or the -CO-NR31R32 radical,

where

R31 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl and

R32 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which they are both bonded, are a pyrrolidino, piperidino or morpholino radical,

R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where

R41 is a suitable oxygen protecting group,

or where

R4a is hydroxyl, and R5a, R4b and R5b are each hydrogen,

Arom is a mono- or bicyclic aromatic radical which is substituted by R6, R7, R8 and R9 and is selected from the group consisting of phenyl, furanyl (furyl) and thiophenyl (thienyl),

where

R6 is hydrogen, C_{1-4}-alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylcarbonyl, carboxyl, C_{1-4}-alkoxy-carbonyl, halogen, hydroxyl, trifluoromethyl, C_{1-4}-alkylcarbonylamino, C_{1-4}-alkoxycarbonyl-amino, C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonylamino or sulphonyl,

R7 is hydrogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

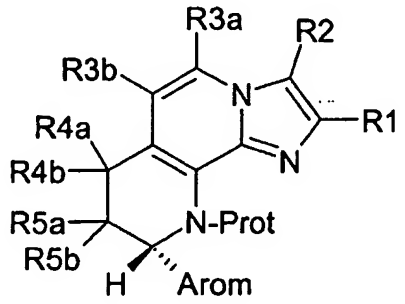
R8 is hydrogen and

R9 is hydrogen,

Prot is an amino protecting group,

and their salts.

Among the compounds according to the invention, emphasis is given to the optically pure compounds of the formula 1*



(1*)

and their salts.

Particular emphasis is given to compounds of the formula 1* where

R1 is hydrogen, methyl, cyclopropyl, methoxymethyl or trifluoromethyl,

R2 is hydrogen, methyl, chlorine, bromine, ethynyl or trifluoromethyl,

R3a is hydrogen,

R3b is hydrogen, fluorine, methyl or the -CO-N$(CH_3)_2$ radical,

R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where

R41 is a suitable oxygen protecting group,

or where

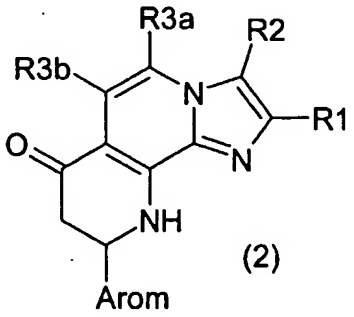
R4a is hydroxyl, and R5a, R4b and R5b are each hydrogen,

Arom is a phenyl radical and

Prot is an amino protecting group,
and their salts.

Preference is given to compounds of the formula 1* where
R1 is methyl,
R2 is methyl,
R3a is hydrogen,
R3b is hydrogen,
R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where
R41 is a suitable oxygen protecting group,
or where
R4a is hydroxyl and R5a, R4b and R5b are each hydrogen,
Arom is a phenyl radical and
Prot is an amino protecting group,
and their salts.

The compounds of the formula 1 according to the invention where R1, R2, R3a, R3b, Arom and Prot are each as defined above, and R4a is R41-O, R5a is hydrogen and R4b and R5b together are a bond may be prepared from the compounds of the formula 2



(2)

by introducing the protecting groups R41 and Prot in a suitable manner. The way in which the protecting groups are introduced depends on their type and is familiar to those skilled in the art on the basis of their knowledge. In a preferred embodiment of the invention, the R41 and Prot groups are identical, so that these groups can be introduced at the same time in one reaction step. When R41 and Prot are each an acetyl group, the reaction of compounds of the formula 2 may be carried out, for example, with acetyl chloride, or preferably with acetic anhydride under suitable conditions.

The compounds of the formula 1 according to the invention where R1, R2, R3a, R3b, Arom and Prot are each as defined above, and R4a is hydroxyl and R5a, R4b and R5b are each hydrogen may be prepared from the compounds of the formula 1 in which R4a is R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where R41 is a suitable oxygen protecting group, by reduction with a suitable reducing agent. An example of a suitable reducing agent is sodium borohydride.

The compounds of the formula 1 according to the invention where R1, R2, R3a, R3b, Arom and Prot are each as defined above, and R4a and R5a are each hydrogen, and R4b and R5b together are a bond may be prepared from the compounds of the formula 1 in which R4a is hydroxyl, and R5a, R4b and R5b are each hydrogen, by elimination (dehydration) in a manner known per se, preferably under acid catalysis and/or using a suitable dehydrating agent (see, for example, Patai-Rappaport, The Chemistry of the Hydroxyl Group, Vol. 2, pp. 641-718, New York, Wiley 1971).

The compounds of the formula 1 according to the invention are valuable precursors and intermediates for preparing tetrahydroimidazo[1,2-h][1,7]naphthyridines, as described, for example, in the International Patent Applications WO 98/42707, WO 00/17200, WO 00/26217, WO 00/63211, WO 01/72756, WO 01/72754, WO 01/72757 and WO 02/34749. Exemplary conversions of compounds of the formula 1 to the abovementioned tetrahydroimidazo[1,2-h][1,7]naphthyridines are described in the examples.

The compounds of the formula 2 are known or may be prepared starting from appropriate starting compounds using similar process steps (see, for example, WO 01/72756, scheme 2 where G = hydrogen) as described exemplarily in the examples which follow herein below.

The examples which follow serve to illustrate the invention without limiting it. Equally, further compounds of the formula 1 whose preparation is not explicitly described may be prepared in a similar manner or a manner familiar to those skilled in the art using customary process techniques. The abbreviation min represents minute(s), h represents hour(s) and m.p. represents melting point.

Examples

End products of the formula 1

1. *rac*-7-Acetoxy-10-acetyl-2,3-dimethyl-9-phenyl-9,10-dihydroimidazo[1,2-h][1,7]naphthyridine

90.0 g (0.31 mol) of *rac*-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridin-7-one are suspended in 250 ml of acetic anhydride and admixed with 20 ml of methanesulphonic acid. The mixture is then heated to reflux for 3 h. After cooling, the acetic anhydride is distilled off under reduced pressure and the oily residue is added to 200 ml of water. The pH of the mixture is adjusted to pH 9 by adding concentrated ammonia solution with stirring. After adding 200 ml of water, extraction is effected using methylene chloride. The organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue is crystallized using diethyl ether, and the precipitate is filtered off with suction and washed with diethyl ether. 85.4 g (74%) of the title compound are isolated as a yellow solid (m.p. 237-239°C).

2. (9*S*)-7-Acetoxy-10-acetyl-2,3-dimethyl-9-phenyl-9,10-dihydroimidazo[1,2-h][1,7]naphthyridine

8.7 g (0.03 mol) of (9*S*)-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridin-7-one are suspended in 49 ml of acetic anhydride, admixed with 2 ml of methanesulphonic acid and heated to reflux. After 30 min, another 2 ml of methanesulphonic acid are added. After 1 h, the reaction mixture is added to 250 ml of ice-water and neutralized by adding concentrated ammonia solution. Extraction is effected using methylene chloride, and the organic phase is dried over magnesium sulphate and evaporated. The residue is crystallized using diethyl ether, and the precipitate is filtered off with suction and washed with diethyl ether. 7.2 g (65%) of the title compound are isolated as a yellow solid (m.p. 237-239°C).

3. *rel*-(7*S*,9*S*)-10-Acetyl-7-hydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2h][1,7]-naphthyridine (racemic)

12.2 g (32.5 mmol) of *rac*-7-acetoxy-10-acetyl-2,3-dimethyl-9-phenyl-9,10-dihydroimidazo[1,2-h][1,7]-naphthyridine are dissolved in 50 ml of methanol and 10 ml of dichloromethane. 5.0 g (132 mmol) of sodium borohydride are then introduced at 0°C over a period of 2 h. After 3 h, 30 ml of saturated ammonium chloride solution are added. The reaction mixture is extracted using dichloromethane, and the organic phase is dried over magnesium sulphate and evaporated. The residue is crystallized using diethyl ether. 8.2 g (75%) of the title compound are isolated as a colorless solid (m.p. 217°C).

4. *rac*-10-Acetyl-2,3-dimethyl-9-phenyl-9,10-dihydroimidazo[1,2-h][1,7]naphthyridine (racemic)

6.0 g (17.9 mmol) of *rel*-(7*S*,9*S*)-10-acetyl-7-hydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridine (racemic) are dissolved in 100 ml of dichloromethane and 20 ml of triethylamine. A solution of 2.9 g (25 mmol) of methanesulphonyl chloride in 5 ml of dichloromethane is then added dropwise with ice cooling within 30 min. After 2 h, hydrolysis is effected using water and extraction using dichloromethane. The organic phase is dried over magnesium sulphate and evaporated. The residue is crystallized using diethyl ether. 4.8 g (85%) of the title compound are isolated as a pale brown solid (m.p. 170°C).

Use of compounds of the formula 1 according to the invention for preparing active ingredients having a tetrahydroimidazo[1,2-h][1,7]naphthyridine structure

A. (8*R*,9*R*)-10-Acetyl-8-hydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]-naphthyridin-7-one

2.0 g (5.4 mmol) of (9*S*)-7-acetoxy-10-acetyl-2,3-dimethyl-9-phenyl-9,10-dihydroimidazo[1,2-h][1,7]-naphthyridine are dissolved in 30 ml of acetone and 6 ml of water. 1.0 g (6.4 mmol) of potassium permanganate is then introduced in portions at 0°C. After 30 min, the brown suspension is admixed with 1 ml of saturated sodium hydrogensulphite solution, filtered through Celite and washed with methanol and dichloromethane. The filtrate is concentrated and the residue crystallized using ethanol. 0.3 g (16%) of the title compound is isolated as a yellow solid (m.p. 192°C).

B. (7*R*,8*R*,9*R*)-10-Acetyl-7,8-dihydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridine

0.2 g (0.6 mmol) of (8*R*,9*R*)-10-acetyl-8-hydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridin-7-one is dissolved in 15 ml of methanol and admixed with 40 mg (1.1 mmol) of sodium borohydride in portions with ice cooling. After 10 min, hydrolysis is effected using saturated sodium hydrogencarbonate solution and extraction using dichloromethane. The organic phase is dried over magnesium sulphate and evaporated. The residue is crystallized using diethyl ether. 0.16 g (80%) of the title compound is isolated as a colourless solid (m.p. 260-261°C).

C. (7*R*,8*R*,9*R*)-7,8-Dihydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]-naphthyridine

The N-acetyl protecting group is detached from the compound (7*R*,8*R*,9*R*)-10-acetyl-7,8-dihydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridine by heating with potassium

carbonate in 2-aminoethanol (temp. 70-100°C). After extractive workup and crystallization, the title compound is obtained as a colourless solid of m.p. 206-209°C.

Starting compounds

AA. (9*S*)-2,3-Dimethyl-9-phenyl-5,6,7,8,9,10-hexahydroimidazo[1,2-h][1,7]naphthyridin-7-one

9.7 g (51.6 mmol) of ethyl (*S*)-3-amino-3-phenylpropionate, 8.5 g (51.6 mmol) of 2,3-dimethyl-6,7-dihydro-5*H*-imidazo[1,2-a]pyridin-8-one and 0.26 g (1.3 mmol) of p-toluenesulphonic acid monohydrate are heated to reflux in 50 ml of toluene using a water separator. After no more water separates, the reaction mixture is cooled to 0°C and diluted with 100 ml of tetrahydrofuran. 7.24 g (64.5 mmol) of potassium *tert*-butoxide are then introduced and the mixture is stirred at room temperature for 16 h. 150 ml of saturated ammonium chloride are added to the reaction mixture, the organic phase is removed and the aqueous phase is extracted with 300 ml of ethyl acetate. The combined organic phases are washed with 250 ml of water, dried over sodium sulphate and evaporated. 13.27 g (88%) of the title compound are isolated as a red-brown oil. An analytical sample is obtained by crystallizing with diethyl ether (red solid, m.p. 134°C).

BB. (9*S*)-2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridin-7-one

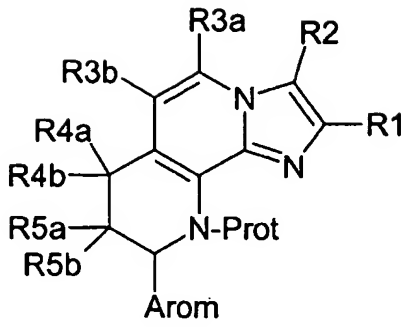
63.5 g (0.22 mol) of (9*S*)-2,3-dimethyl-9-phenyl-5,6,7,8,9,10-hexahydroimidazo[1,2-h][1,7]naphthyridin-7-one are dissolved in 250 ml of toluene and 250 ml of tetrahydrofuran, and cooled to 0°C. 59 g (0.26 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone are introduced in portions of 10 g over a period of 1 h with mechanical stirring. The reaction mixture is stirred at room temperature for 16 h. 1.2 l of 0.5 N sodium hydroxide solution and 1 l of ethyl acetate are then added dropwise. The organic phase is removed and washed with water. The aqueous phase is reextracted with ethyl acetate, and the combined organic phases are dried over sodium sulphate and evaporated. The residue is crystallized at 0°C in 300 ml of methanol. The solid is filtered off with suction, washed with cold methanol and dried. 20 g (32%) of the title compound are isolated as a pale yellow solid (m.p. 103-105°C).

Commercial applicability

The compounds of the formula 1 and their salts are valuable intermediates for preparing active ingredients, as disclosed, for example, in the International Patent Applications WO 98/42707, WO 00/17200, WO 00/26217, WO 00/63211, WO 01/72756, WO 01/72754, WO 01/72757 and WO 02/34749.

Claims

1. Compounds of the formula 1



(1)

where

R1 is hydrogen, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkoxycarbonyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, fluoro-C_{1-4}-alkyl or hydroxy-C_{1-4}-alkyl,

R2 is hydrogen, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-4}-alkyl, C_{1-4}-alkoxycarbonyl, hydroxy-C_{1-4}-alkyl, halogen, C_{2-4}-alkenyl, C_{2-4}-alkynyl, fluoro-C_{1-4}-alkyl or cyanomethyl,

R3a is hydrogen, halogen, fluoro-C_{1-4}-alkyl, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{1-4}-alkoxy, carboxyl, C_{1-4}-alkoxycarbonyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkoxy-C_{1-4}-alkyl, fluoro-C_{1-4}-alkoxy-C_{1-4}-alkyl or the -CO-NR31R32 radical,

R3b is hydrogen, halogen, fluoro-C_{1-4}-alkyl, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{1-4}-alkoxy, carboxyl, C_{1-4}-alkoxycarbonyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkoxy-C_{1-4}-alkyl, fluoro-C_{1-4}-alkoxy-C_{1-4}-alkyl or the -CO-NR31R32 radical,

where

R31 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl and

R32 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which they are both bonded, are a pyrrolidino, piperidino or morpholino radical,

R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where

R41 is a suitable oxygen protecting group,

or where

R4a is hydroxyl, and R5a, R4b and R5b are each hydrogen,

Arom is a mono- or bicyclic aromatic radical which is substituted by R6, R7, R8 and R9 and is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,

where

R6 is hydrogen, C_{1-4}-alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{2-4}-alkenyloxy, C_{1-4}-alkylcarbonyl, carboxyl, C_{1-4}-alkoxycarbonyl, carboxy-C_{1-4}-alkyl, C_{1-4}-alkoxycarbonyl-C_{1-4}-alkyl, halogen, hydroxyl, aryl, aryl-C_{1-4}-alkyl, aryloxy, aryl-C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, mono- or

di-C_{1-4}-alkylamino, C_{1-4}-alkylcarbonylamino, C_{1-4}-alkoxycarbonylamino, C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonylamino or sulphonyl,

R7 is hydrogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

R8 is hydrogen, C_{1-4}-alkyl or halogen and

R9 is hydrogen, C_{1-4}-alkyl or halogen,

where

aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group of C_{1-4}-alkyl, C_{1-4}-alkoxy, carboxyl, C_{1-4}-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

Prot is an amino protecting group,

and their salts.

2. Compounds of the formula 1 according to Claim 1, where

R1 is hydrogen, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl, C_{2-4}-alkynyl or fluoro-C_{1-4}-alkyl,

R2 is hydrogen, C_{1-4}-alkyl, halogen, C_{2-4}-alkenyl, C_{2-4}-alkynyl or fluoro-C_{1-4}-alkyl,

R3a is hydrogen,

R3b is hydrogen, halogen, C_{1-4}-alkyl or the -CO-NR31R32 radical,

where

R31 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl and

R32 is hydrogen, C_{1-7}-alkyl, hydroxy-C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{1-4}-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which they are both bonded, are a pyrrolidino, piperidino or morpholino radical,

R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where

R41 is a suitable oxygen protecting group,

or where

R4a is hydroxyl, and R5a, R4b and R5b are each hydrogen,

Arom is a mono- or bicyclic aromatic radical which is substituted by R6, R7, R8 and R9 and is selected from the group consisting of phenyl, furanyl (furyl) and thiophenyl (thienyl),

where

R6 is hydrogen, C_{1-4}-alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylcarbonyl, carboxyl, C_{1-4}-alkoxy-carbonyl, halogen, hydroxyl, trifluoromethyl, C_{1-4}-alkylcarbonylamino, C_{1-4}-alkoxycarbonyl-amino, C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonylamino or sulphonyl,

R7 is hydrogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

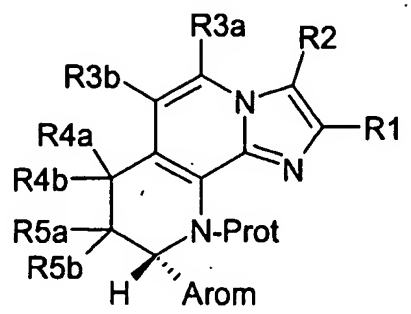
R8 is hydrogen and

R9 is hydrogen,

Prot is an amino protecting group,

and their salts.

3. Optically pure compounds according to Claim 1, characterized by the formula 1*



(1*)

where R1, R2, R3a, R3b, R4a, R4b, R5a, R5b, Arom and Prot are each as defined in Claim 1, and their salts.

4. Compounds of the formula 1* according to Claim 3, where

R1 is hydrogen, methyl, cyclopropyl, methoxymethyl or trifluoromethyl,

R2 is hydrogen, methyl, chlorine, bromine, ethynyl or trifluoromethyl,

R3a is hydrogen,

R3b is hydrogen, fluorine, methyl or the -CO-N(CH_3)$_2$ radical,

R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where

R41 is a suitable oxygen protecting group,

or where

R4a is hydroxyl, and R5a, R4b and R5b are each hydrogen,

Arom is a phenyl radical and

Prot is an amino protecting group,

and their salts.

5. Compounds of the formula 1* according to Claim 3, where

R1 is methyl,

R2 is methyl,

R3a is hydrogen,

R3b is hydrogen,

R4a is hydrogen or R41-O, R5a is hydrogen, and R4b and R5b together are a bond, where

R41 is a suitable oxygen protecting group,

or where

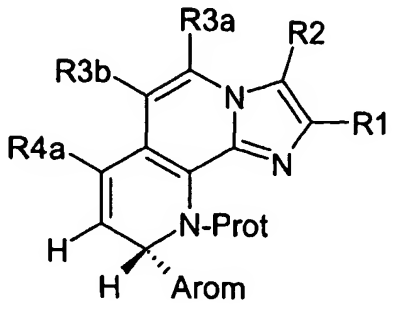
R4a is hydroxyl and R5a, R4b and R5b are each hydrogen,

Arom is a phenyl radical and

Prot is an amino protecting group,

and their salts.

6. Optically pure compounds according to Claim 1, characterized by the formula 1**



(1**)

where

R1 is hydrogen, methyl, cyclopropyl, methoxymethyl or trifluoromethyl,

R2 is hydrogen, methyl, chlorine, bromine, ethynyl or trifluoromethyl,

R3a is hydrogen,

R3b is hydrogen, fluorine, methyl or the -CO-N(CH_3)$_2$ radical,

R4a is hydrogen or R41-O, where

R41 is a suitable oxygen protecting group,

Arom is a phenyl radical and

Prot is an amino protecting group,

and their salts.

7. Compounds of the formula 1** according to Claim 6, where

R1 is methyl,

R2 is methyl,

R3a is hydrogen,

R3b is hydrogen,

R4a is hydrogen or R41-O, where

R41 is a suitable oxygen protecting group,

Arom is a phenyl radical and

Prot is an amino protecting group,

and their salts.

8. Compounds of the formula 1** according to Claim 6 or 7, where

R4a is hydrogen, and their salts.

9. Compounds of the formula 1** according to Claim 6 or 7, where

R41 and Prot are identical and are selected from the group consisting of C_{1-4}-alkylcarbonyl, C_{1-4}-alkoxycarbonyl and C_{1-4}-alkoxy-C_{1-4}-alkoxycarbonyl, and their salts.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01349

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/14 //A61K31/4375,A61P1/00,(C07D471/14,235:00,221:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 26217 A (BYK GULDEN LOMBERG) 11 May 2000 (2000-05-11) claim 1	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2003	12/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[redacted]al Application No
PCT/EP 03/01349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0026217 A	11-05-2000	AU 1044500 A	22-05-2000
		CA 2349476 A1	11-05-2000
		WO 0026217 A1	11-05-2000
		EP 1127059 A1	29-08-2001
		JP 2002528548 T	03-09-2002
		US 6384048 B1	07-05-2002